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Eculizumab in atypical hemolytic-uremic syndrome

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[CI], 0.57 to 0.83) for the first 21 days, 1.00 (95% CI, 0.57 to 1.76) for 22 to 60 days, and 0.38 (95% CI, 0.18 to 0.82) for 61 to 90 days. We also await results of trials such as POINT and TARDIS for confirmation of these results in non-Chinese populations.

We agree with Jeong that there may be important differences according to the patients' ethnicity and environment that limit the generalizability of our results, and we await the results of future clinical trials.

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Since publication of their article, the authors report no further potential conflict of interest.

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Ecuzumab in Atypical Hemolytic–Uremic Syndrome

TO THE EDITOR: With regard to the article by Legendre et al. (June 6 issue)¹: assessment of the 37 patients with atypical hemolytic–uremic syndrome is difficult, since the process of selection seems opaque, particularly for the 20 patients in trial 2. It would have been beneficial to have these patients undergo randomization, given the fluctuating, relapsing nature of the underlying disease. In trial 1, a shorter delay before administration of the first dose of ecuzumab was reported to result in a better recovery of renal function. My colleagues and I evaluated these data with consideration of the delay before administration of ecuzumab and of the change in creatinine values; our findings provided a different answer (Fig. 1). Omitting an outlier with a delay of 96 days, we found a correlation coefficient of -0.20 ($P=0.50$).

The article states, “atypical hemolytic–uremic syndrome is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy,” yet 24 to 30% of the study patients had no proven genetic disease, and proof of ongoing complement activation was lacking, except for the alleged effect of ecuzumab. Methods to detect ongoing complement activation in patients with this rare condition are being developed²; 20% of these patients are reported to be hematologically normal at presentation.³ Not all patients with atypical hemolytic–uremic syndrome have a straightforward response to ecuzumab, and explanations other than complement activation may be relevant.^{4,5}

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No potential conflict of interest relevant to this letter was reported.

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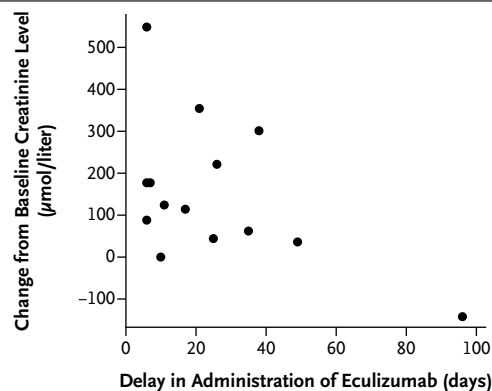


Figure 1. Scatter Plot of the Change in Creatinine Level in Relation to the Delay before the Administration of Ecuzumab.

The change in the creatinine level from baseline to 64 weeks (see section 4 in the Supplementary Appendix, available with the full text of the article by Legendre et al. at NEJM.org) and the delay before the administration of ecuzumab (section 2 in the Supplementary Appendix of the article) are shown. For all included patients (two patients with data that were measured only at baseline and one patient who received continuous hemodialysis were excluded), the correlation coefficient was -0.51 ($P=0.06$). Exclusion of the outlier at the extreme right side of the figure yields a correlation coefficient of -0.20 ($P=0.50$). Each dot represents one patient.

genes in atypical haemolytic-uremic syndrome (aHUS). *Virchows Arch* 2013;462:455-64.

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TO THE EDITOR: We have some concerns about the use of eculizumab for the treatment of atypical hemolytic-uremic syndrome.

Our first concern is the use of the EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) scale to measure health-related quality of life. After reading the relevant cited studies,^{1,2} we were still unable to determine how the authors came to the conclusion that a 0.06 change on the scale was clinically important, and we would like to know how the number was derived.

Second, the authors reported a significant reduction in the number of outcome events (plasma exchange or infusion, dialysis, or both) from approximately one event to no events per day, but we would like to see the absolute numbers of the end points that make up this composite. In particular, which component of the composite drove the outcome?

Finally, we are concerned that the definition of progressive thrombotic microangiopathy in the first study preferentially selected for patients who would have the largest increase in the platelet count after receiving therapy. Were any other signs or symptoms considered for the definition of progressive thrombotic microangiopathy, or were only platelets used?

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TO THE EDITOR: In their study of eculizumab treatment for atypical hemolytic-uremic syndrome, Legendre et al. used a fixed-dose schedule without adjustment for patient weight. We recently administered this regimen to a patient who weighed 95 kg. Despite treatment initiated with

the first episode of atypical hemolytic-uremic syndrome, he had an incomplete hematologic response and remained dependent on dialysis, even though a kidney biopsy performed just before treatment initiation did not show signs of irreversible damage. Drug monitoring revealed a trough level of 71.2 μg per milliliter, which was clearly below the level reported in all study patients, and residual serum complement activity was 12% at day 14 after a 1200-mg dose. I suspect that insufficient eculizumab dosing due to a high body weight may have contributed to the lack of renal recovery in our patient, and I doubt whether one eculizumab dose fits all patients. Unfortunately, because Legendre et al. did not report on patient weights, generalizability of the reported dosing scheme remains unclear. Did achieved drug levels inversely correlate with patient weight, and was there a trend toward a reduced treatment response in patients with high body weight, low eculizumab trough levels, or both?

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TO THE EDITOR: Though Legendre et al. report that the use of eculizumab resulted in increases in the platelet count and improved renal function in patients with atypical hemolytic-uremic syndrome, it is crucial to explore the most appropriate dose, dosage intervals, and duration of treatment to reduce the enormous financial burden of this therapy.

Eculizumab blocks the cleavage of the C5 complement protein to C5a and C5b, and it prevents the generation of the proinflammatory peptide C5a and the membrane-attack complex C5b-9. Traditional markers of thrombotic microangiopathy, such as lactate dehydrogenase or haptoglobin levels, may not be sensitive enough to determine whether the terminal complement pathway is adequately blocked. Monitoring of complement blockade may be used to adjust the dose or the interval between doses of eculizumab therapy to the necessary minimum and may lead to cost reduction. Although inhibition of complement activity is shown in Figure 2D of the article, is the method useful in daily clinical practice? We would be grateful if the authors

could share laboratory markers for assessing the degree of complement blockade.

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THE AUTHORS REPLY: Ring questions the inclusion of patients without identified complement gene mutations, as well as the single-group design and the effects of earlier intervention. Accumulating evidence provides support for the genetic basis of atypical hemolytic-uremic syndrome. The number of identified complement mutations has increased from 109 in 2008 (the year of the trial initiation) to 604 in 2013. No mechanism beyond complement dysregulation has been proposed to explain the pathogenesis of atypical hemolytic-uremic syndrome in adult patients. Given the chronic, progressive, life-threatening nature of atypical hemolytic-uremic syndrome and the unpredictable risk of permanent end-organ damage among patients treated with plasma exchange, infusion, or both, randomization was considered to be neither possible nor ethical. Long-term plasma exchange, infusion, or both are associated with substantial morbidity.¹⁻³ Trial 2 was designed on the basis of data on patients receiving such long-term treatment. The admission criteria and baseline characteristics of the patients in both trials were included in the article. Further, earlier intervention led to significantly greater improvements in the estimated glomerular filtration rate, as shown by an analysis of variance with appropriate correction.

Amadio and Tejani question the use of the EQ-5D scale in assessing quality of life. The minimally important difference of 0.06 was chosen after consultation with leading experts.⁴ With regard to the end points in both trials: all components of the composite end points showed improvement and contributed equally to the results. In trial 1, patients with progressive thrombotic microangiopathy at screening included patients with decreased platelet counts despite four or more sessions of plasma exchange or in-

fusion in the previous week, thrombotic thrombocytopenia, microangiopathic hemolysis, and increased creatinine levels, as detailed in the article.

Kistler queries whether drug levels inversely correlated with weight and affected outcomes. Across both trials, five patients weighed more than 90.0 kg (mean, 96.4 kg; median, 104.0 kg; range, 90.2 to 127.3 kg). Of these patients, eculizumab concentrations were consistently greater than 50 μ g per milliliter in four patients. Most trial end points were met; this showed sustained control of the thrombotic microangiopathy.

Tanimoto et al. call for monitoring of complement levels to decrease the dosage of eculizumab, the dosage interval, and the duration of treatment. One study showed that treatment regimens for atypical hemolytic-uremic syndrome that deviate from dosing approved by the Food and Drug Administration may lead to complications and rapid progression to end-stage renal disease.³ We agree that markers such as the lactate dehydrogenase level, haptoglobin level, and platelet count are insufficiently sensitive for monitoring purposes, as evidenced by significant renal improvement in trial 2 (which included patients with a normal baseline lactate dehydrogenase level and platelet count). However, the lack of standardization and validation of available complement assays currently makes them unsuitable for clinical use. Given the risks of disease progression, the study dosing regimen was designed by both investigators and regulatory agencies to ensure that 95% of patients or more had complete and sustained terminal complement inhibition, even during episodes of increased complement activity (e.g., infection or surgery).

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Mental Health and the Global Agenda

TO THE EDITOR: Becker and Kleinman (July 4 issue)¹ highlight the burden of mental diseases worldwide. Major concerns are for people living in less-developed countries (because of the low level of resources devoted to neuropsychiatric illnesses) and for young people (because of the difficulty accessing mental care).

We would like to emphasize the enormous suffering associated with mental disorders in older people. The prevalence of mental diseases in older people has increased dramatically in the past decades, not only because of aging itself (e.g., Alzheimer's disease), but also because of new emotional and sociodemographic situations to which the elderly are exposed.² Moreover, disorders such as depression and dysthymia often become chronic, and the link between mental and physical health (ultimately leading to disability) is extremely strong.³ Finally, the use of psychotropic medications without fair evidence of safety, efficacy, and effectiveness in persons who are already receiving many other medications is fraught with danger. Training primary care clinicians in the care of elderly patients with mental illness should be a priority.

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TO THE EDITOR: In their article, Becker and Kleinman articulate the critical steps needed to improve global mental health care. One of us is a Ghanaian medical student, and we would respectfully add that persons involved in the discourse on global mental health also need to en-

gage indigenous mental health care systems. These systems, which fall outside the hegemonic discourse of Western psychiatry, include traditional healers and faith-based practitioners. In Ghana, it is estimated that there are 45,000 traditional "healers" — far more than there are psychiatrists, psychologists, social workers, and mental health nurses.¹ These indigenous forms of healing are widely used, in part, because they operate within ingrained cultural beliefs about mental illnesses,² and although there is limited research, there is some evidence that traditional healers are effective in offering certain mental health services.³ Although legitimate concerns have been raised about human rights abuses and the scientific validity of forms of treatment in traditional medicine, these caregivers shoulder a considerable burden of care delivery and offer an important avenue through which capacity can be developed, stigma can be reduced, and quality can be improved.

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THE AUTHORS REPLY: Marengoni and Pecorelli raise an important point about the large and growing mental health burden in older persons. Indeed, the formidable burden imposed by Alz-